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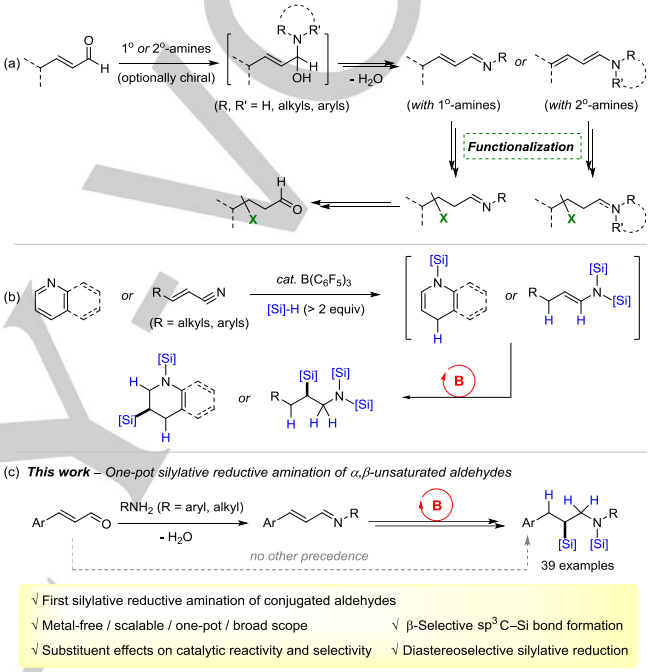
Silylative Reductive Amination of α,β-Unsaturated Aldehydes: A Convenient Synthetic Route to β-Silylated Secondary Amines

Eunae Kim, Sehoon Park,* and Sukbok Chang*

Abstract: *Described herein is a reductive amination/hydrosilylation cascade of α,β-unsaturated aldehydes mediated by a Lewis acidic borane catalyst. The present reaction system provides an one-pot synthetic route towards β-silylated secondary amines that have not been accessible via other precedent catalysis. Comparative ^{1}H NMR studies on the silylative reduction of enimines revealed that steric bulkiness of primary amine reactants strongly affects both catalytic efficiency and regioselectivity. This strategy was applicable to a broad range of substrates and amenable to one-pot gram-scale synthesis. Moreover, a diastereoselective introduction of the β-silyl group was also found to be feasible (dr. up to 71:29).*

α,β-Unsaturated carbonyls are highly useful building blocks in organic synthesis.[1] This is probably due to their versatile reactivities based on a LUMO-lowering activation pathway.[2] Given such an intrinsic electronic property, α,β-unsaturated carbonyls undergo conjugate addition by a number of nucleophilic organo(metallic) compounds, providing formally reduced products to form a new sp^3 carbon-Nu bond (Nu: = nucleophiles based on H, C, N, etc.).[3] Among various transformations, remote functionalization of α,β-unsaturated aldehydes via enimines or dienamines as a key intermediate has drawn a considerable attention in (asymmetric) organic synthesis (Scheme 1a).[4-5] Despite of such numerous utilization of α,β-unsaturated carbonyls, there have been no reports on the reductive amination[6] of α,β-unsaturated carbonyls *leading to silylated amines*.

On the other hand, we previously reported the boron-catalyzed silylative reduction of quinolines, pyridines, and conjugated nitriles, affording a diverse range of aza compounds having a sp^3 C–Si bond *beta* to the nitrogen atom (Scheme 1b).[7]



Scheme 1. a) Functionalizations of α,β-unsaturated aldehydes via enimines or dienamines. b) $B(C_6F_5)_3$-catalyzed silylative reduction cascades of pyridines and conjugated nitriles. c) Silylative reductive amination of conjugated aldehydes leading to β-silylated secondary amines (this work).

In mechanistic studies, we found that the β-silylation takes place via an enamine intermediate formed by an initial $B(C_6F_5)_3$-mediated 1,4-hydrosilylation.

In this context, we envisioned that α,β-unsaturated aldimines that can be conveniently generated through a condensation reaction of conjugated aldehydes with primary amines, would undergo a C(sp^3)–Si bond-forming reduction cascade under the $B(C_6F_5)_3$ catalysis.[8] Described herein is the silylative reductive amination of α,β-unsaturated aldehydes, providing β-silylated secondary amines in one-pot (Scheme 1c). *This work represents the first example of reductive amination with concomitant incorpotation of a silyl group*. A variety of combinations of readily accessible aldehydes and primary amines enabled us to synthesize a wide range of β-silylated amines in high yields. The reaction path of a silylative reduction of conjugated imines were elucidated: an *N*-bulky substituent of substrates leads to 1,4-hydrosilylation, while a less bulky group on the N atom causes the formation of 1,2-addition intermediate as a minor path. The present one-pot strategy was amenable to the gram-scale synthesis and also to the diastereoselective silylative reduction.

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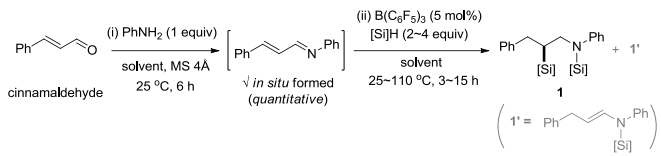
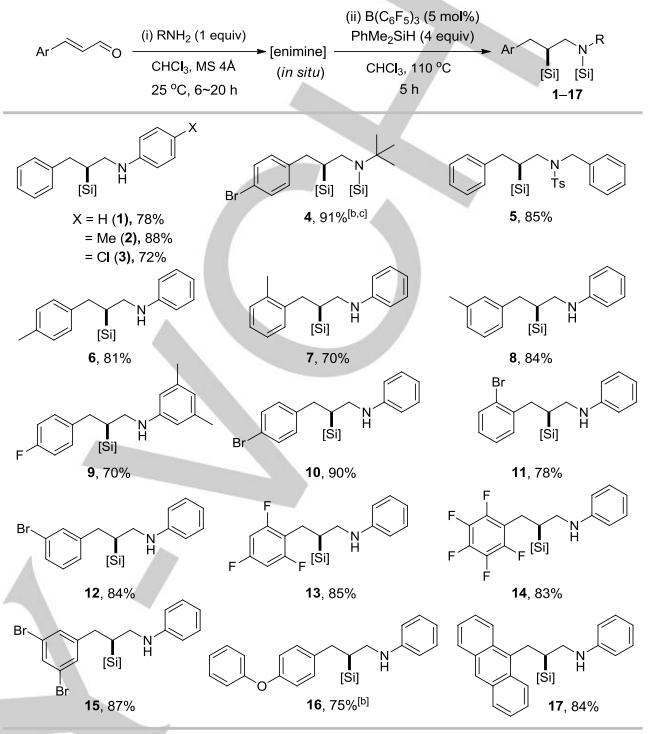
Table 1: Screen of reaction conditions.[a]



Entry	Silane (equiv)	Solvent	*T* [°C]	*t* [h]	Yields of **1/1'**[%][b]
1	$PhMe_2SiH$ (4)	$CDCl_3$	85	6	59/25
2	$PhMe_2SiH$ (4)	$CDCl_3$	85	15	85/<1
3	Et_2SiH_2 (4)	$CDCl_3$	85	15	77/<1
4	Ph_2SiH_2 (4)	$CDCl_3$	85	15	55/<1
5	Et_3SiH (4)	$CDCl_3$	85	15	7/65
6	$PhMe_2SiH$ (4)	$CDCl_3$	25	15	<1/90
7	$PhMe_2SiH$ (4)	$CDCl_3$	45	15	9/73
8	$PhMe_2SiH$ (4)	$CDCl_3$	60	15	33/50
9	$PhMe_2SiH$ (4)	$CDCl_3$	110	3	89/<1
10	$PhMe_2SiH$ (4)	toluene-d_8	110	3	83/<1
11	$PhMe_2SiH$ (4)	benzene-d_6	110	3	86/<1
12	$PhMe_2SiH$ (4)	C_6D_5Cl	110	3	78/<1
13	$PhMe_2SiH$ (2)	$CDCl_3$	110	3	79/<1
14	$PhMe_2SiH$ (3)	$CDCl_3$	110	3	85/<1

[a] Reaction conditions: for step (i) cinnamaldehyde (0.5 mmol) and aniline (1 equiv) in solvent (0.4 mL) in the presence of molecular sieve 4Å (200 mg) at 25 °C, 6~20 h; for step (ii) $B(C_6F_5)_3$ (0.025 mmol, 5 mol% relative to cinnamaldehyde), silane (1~2 mmol, 2~4 equiv relative to cinnamaldehyde), solvent (0.1 mL) at 25~110 °C, 3~15 h. Conversion of an aldimine was >99%. [b] Determined by ^{1}H NMR of the crude reaction mixture on the basis of 1,1,2,2-tetrachloroethane (TCE) as an internal standard.

Table 2: Scope of silylative reductive amination of α,β-unsaturated aldehydes.[a]



[a] Reaction conditions: for step (i) conjugated aldehydes (0.5 mmol) and anilines (1 equiv) in $CHCl_3$ (0.4 mL) in the presence of molecular sieve 4Å (200 mg) at 25 °C, 6~20 h; for step (ii) $B(C_6F_5)_3$ (0.025 mmol, 5 mol%), $PhMe_2SiH$ (2 mmol, 4 equiv) in $CHCl_3$ (0.1 mL) at 110 °C for 5 h. Isolated as an NH form upon silica-column chromatography. [b] Et_2SiH_2 (4 equiv) used instead of $PhMe_2SiH$. [c] Crude NMR yields determined by ^{1}H NMR on the basis of 1,1,2,2-tetrachloroethane (TCE) as an internal standard.

At the outset of this study, we conducted an optimization study using cinnamaldehyde as a standard substrate for the one-pot silylative reductive amination cascade (Table 1). A condensative reaction of cinnamaldehyde with aniline in the presence of molecular sieve was found to be facile in various solvents to quantitatively afford an enimine (completed in 6 h at 25 °C).[9] Upon completion of the conjugate imine formation, the $B(C_6F_5)_3$/silane system under variable conditions was applied to the *in situ* formed imine solution. The reaction with $PhMe_2SiH$ (4 equiv) in the presence of $B(C_6F_5)_3$ (5 mol%) smoothly proceeded at 85 °C to result in a mixture of N-(2-silyl-3-phenylpropyl)aniline **1** and N-(3-phenyl-1-propenyl)aniline **1'** in 59% and 25% in 6 h, respectively, and the yield of **1** reached up to 85% in 15 h (Table 1, entries 1–2). This result indicates that the cascade reaction proceeds *via* an N-(3-phenyl-1-propenyl)aniline intermediate **1'**. Increasing steric bulkiness of silanes led to lower efficiency: a reaction with Et_2SiH_2 furnished **1** in 77% yield (entry 3), whereas bulkier silanes, Ph_2SiH_2 and Et_3SiH were less reactive to afford **1** in 55% and 7%, respectively (entries 4–5). It is noteworthy that the reaction with Et_3SiH afforded 65% of **1'** as a major product, suggesting that the β-silylation on **1'** is a turnover-limiting step (*vide infra*). Reaction temperature turned out to be crucial to the catalytic efficiency: the reaction at a range of 25 to 60 °C produced **1** in inferior yield but yielded **1'** in 50~90% (entries 6–8), while elevating temperature to 110 °C improved the catalytic efficiency to attain 89% of **1** in 3 h (entry 9). The optimal solvent for both the condensation and silylative steps was next examined: toluene, benzene, and chlorobenzene were viable to give **1** in 78~86% in addition to chloroform (entries 10–12). Reducing the silane quantity brought about slightly lower yield of **1** relative to that with 4 equiv of silane (entries 13–14).[10]

With the optimal conditions in hand, the scope of the one-pot silylation cascade was explored (Table 2). Electronic variation in the aniline moiety had marginal effects in leading β-silylated products (**1**–**3**) in good to high yields. The α,β-unsaturated aldimines obtained from alkyl amines smoothly underwent silylative reduction to furnish **4** and **5** in 91% and 85%, respectively. Notably, facile formation of **4** was achieved when Et_2SiH_2 was employed instead of $PhMe_2SiH$. Next, aryl-substituted acrylaldehydes with electronic and steric variations in the aryl moiety were subjected to the $B(C_6F_5)_3$-catalyzed silylative reduction conditions. The *m*- or *p*-methyl substituted aryl group had no significant effects on the product yields (**1**, 78% *vs.* **6**, 81%; **8**, 84%), while an *o*-methyl substituent in the aryl moiety gave slightly lower yield (**7**, 70%). These results imply that the present catalysis is sensitive to the sterics of the aryl-moiety in substrates (also *vide infra*). The reaction of a series of acrylaldehydes bearing a haloaryl group smoothly proceeded in the presence of $B(C_6F_5)_3$ catalyst to afford the corresponding β-silylated products in 70~90% (**9**–**15**). Substrates having a *p*-phenoxyaryl or anthracene group reacted with $PhMe_2SiH$ to give the desired β-silylated secondary amines in 75% (**16**) and 84% (**17**) respectively, upon silica-column chromatography.[11]

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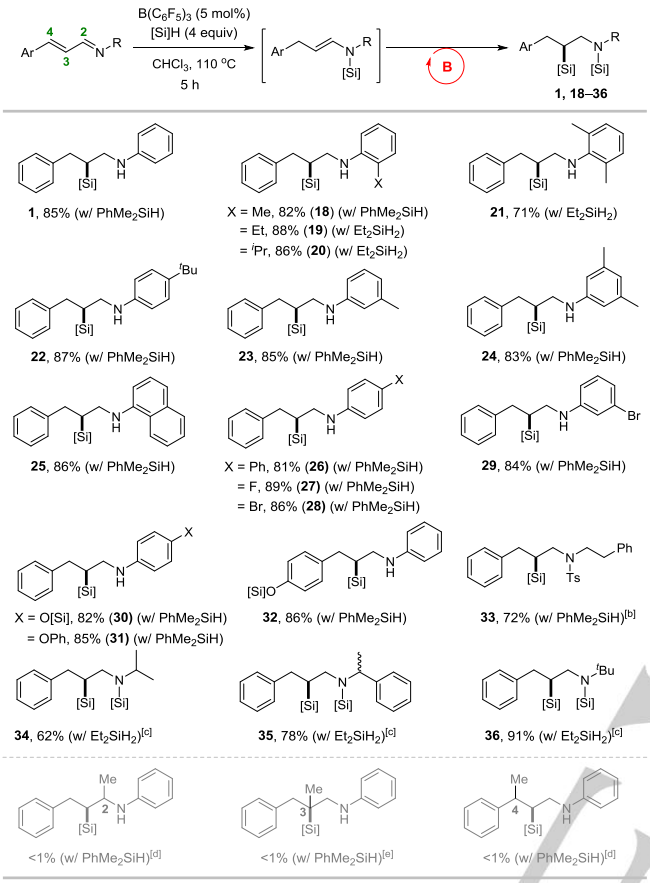
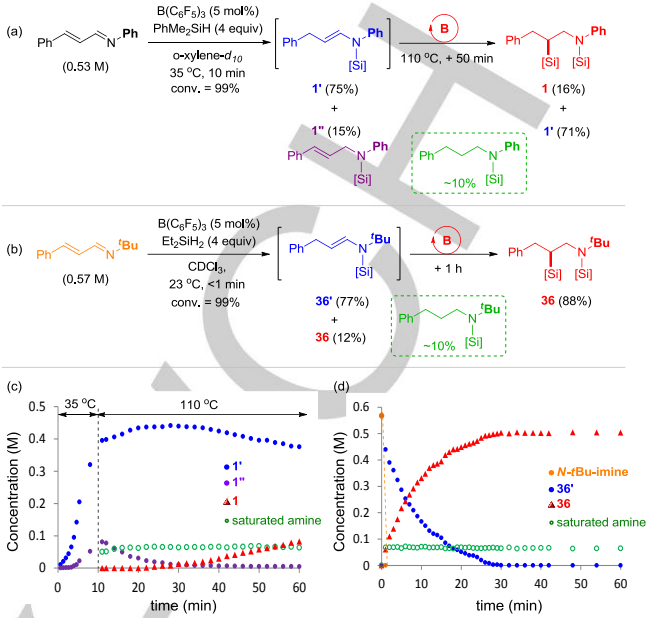
Table 3: Scope of silylative reduction of α,β-unsaturated aldimines.[a]



[a] Reaction conditions: conjugated imines (0.5 mmol), $B(C_6F_5)_3$ (0.025 mmol, 5 mol%), silane (2 mmol, 4 equiv) in $CHCl_3$ (0.5 mL) at 110 °C for 5 h. Isolated as an NH or N-Ts form. [b] Yields over two steps. [c] Crude NMR yields determined by ^{1}H NMR on the basis of 1,1,2,2-tetrachloroethane (TCE) as an internal standard. [d] An exhaustive reduction product as a major was formed. [e] An 1,2-addition product was formed as a major.

To demonstrate the flexibility of the current synthetic route to β-silyl amines, we next examined the $B(C_6F_5)_3$-catalyzed silylative reduction of various α,β-unsaturated aldimines (Table 3). A series of substrates possessing an alkyl-substituted aniline moiety were initially tested. *ortho*-Alkyl substituent(s) on the aniline moiety rendered the reaction sluggish, thus requiring to use Et_2SiH_2, a more reactive hydrosilane reagent to give reasonable yields of the desired products (**18**–**21**, 71~88%). Alkyl substituents at the other position(s) on the aniline unit had a minimal impact, which allowed for smooth conversion (**22**–**24**, 83~87%). Substrates bearing an N-naphthyl or -biphenyl group were also reacted under the standard conditions to give **25** and **26** in 86% and 81%, respectively. The present reaction was found to be almost insensitive to electronic factors since electronic variations in both aniline and aldehyde units brought about all similar product yields comparable to that of **1** (**27**–**32**, 82~89% *vs.* **1**, 85%). Reactions of enimine substrates having a series of *N*-alkyl groups were performed to reveal that Et_2SiH_2 was more effective relative to $PhMe_2SiH$, leading to good to high yields of the desired products **33**–**36** (62~91%). It is noteworthy that a substrate bearing an N-^{t}Bu group was more reactive than substrates bearing a less bulky N-alkyl unit under the identical conditions (**36**, 91% *vs.* **34**, 62%). This result suggests that a borane species that binds to an amine unit is in an off-cycle resting state.[7a-d] Unfortunately, a reaction



Scheme 2. ^{1}H NMR monitoring of the silylative reduction of *N*-phenyl (*a*,*c*) and *N*-tert-butyl (*b*,*d*) enimines under the borane catalysis.

of conjugated imines bearing an alkyl-substituent at the C2 to C4 position did not afford the desired β-silylated amines under the standard conditions. Instead, an exhaustive product lacking a sp^3 C–Si bond was formed from C2- or C4-methyl-enimines, while a C3-methyl substituted enimine was converted mainly to the respective 1,2-addition product.

To understand the reaction behavior in more detail, the silylative reduction of two representative enimine substrates was set for the ^{1}H NMR-led progress monitoring (Scheme 2). The reaction of an *N*-phenyleneimine with $PhMe_2SiH$ (4 equiv) proceeded to attain a quantitative conversion in 10 min at 35 °C, giving rise to a mixture of 1,4-product **1'** (75%) and 1,2-product **1"** (15%). At this stage, the β-silylated product **1** was not formed yet. Upon elevating temperature to 110 °C, the *in situ* formed **1'** begun to slowly be reduced to the β-silylated product **1** (16%) with disappearance of the 1,2-product **1"** over 50 min at 110 °C (Scheme 2a,c). These observations provide some insights: (i) an imine intermediate undergoes mainly 1,4-addition, while 1,2-addition also takes place as a minor path; and (ii) the sp^3 β-C–Si bond formation is rate-limiting.

On the other hand, the reaction of an N-^{t}Bu-imine showed somewhat distinctive reaction profiles (Scheme 2b,d). In fact, this imine was rapidly converted to give a mixture of 1,4-product **36'** (77%) and the desired product **36** (12%) within 1 min. Prolonged reaction up to 1 h at 23 °C, the enamine intermediate **36'** was completely consumed to eventually afford **36** in 88% yield.[12] This result clearly indicates that steric bulkiness of an N-substituent of enimines strongly influences both reaction rate and regioselectivity for the addition of a Si–H bond.

Based on the above observations and our previous reports,[7a-c] a reaction pathway for the $B(C_6F_5)_3$-mediated silylative reduction of α,β-unsaturated aldimines is proposed in Scheme 3. $B(C_6F_5)_3$ catalyst is assumed to form an adduct **A** with an aldimine substrate as a resting species,[13] which is dissociated into an aldimine and an active species of borane-silane adduct **B**.[14] A silyl transfer from **B** to an aldimine substrate will take place to form an iminium ion bearing a borohydride anion **C**. The nucleophilic borohydride attack is presumed to occur selectively at the C-4

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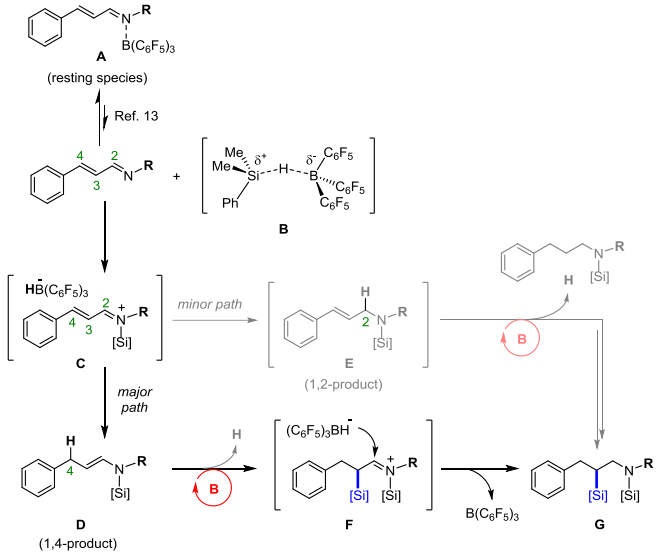


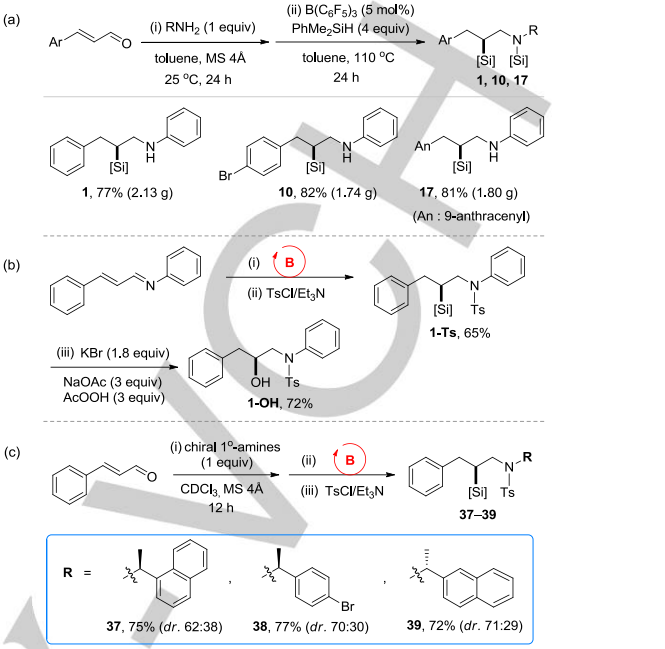
Scheme 3. Proposed mechanism of the $B(C_6F_5)_3$-catalyzed hydrosilylation cascade of α,β-unsaturated aldimines.

position of **C** to form an enamine species **D** when the N-substituent is bulky (*e.g.* R = ^{t}Bu). However, when the N-substituent is less bulky (*e.g.* R= Ph), a hydride transfer to the C-2 position will also take place as a minor path leading to the formation of an allylamine **E**.[13a] The 1,4-addition intermediate **D** is suggested to undergo the turnover-limiting β-selective hydrosilylation *via* an intermediate **F** to give **G**, while the 1,2-addition intermediate **E** is assumed to be hydrosilylated to furnish **G** as well. The saturated amine **H** as a minor product is considered to be formed through intermediates **D** and **E**.[15]

Finally, the synthetic utility of the present catalysis was explored (Scheme 4). The one-pot silylative reductive amination cascade could be carried out on a gram-scale without difficulty to provide a series of β-silylated secondary amines (**1**, **10**, and **17)** in 77~82% yields (Scheme 4a). **1** synthesized from the parent aldimine under the borane catalysis was subjected to the Fleming-Tamao oxidation conditions,[16] giving rise to an *N*-tosylated β-amino alcohol (**1-OH**) in 47% total yield (Scheme 4b).

The one-pot diastereoselective silylative reduction was briefly attempted by employing α,β-unsaturated aldimines bearing an enantiomerically enriched amine unit. While a series of β-silylated products (**37–39**) were obtained with moderate diastereomeric ratios (up to 71:29) at the present stage, further comprehensive screening of the chiral anciliaries may allow us to achieve high diastereoselectivity of the β-silylated amines (Scheme 4c).

In summary, we have for the first time developed the silylative reductive amination cascade of α,β-unsaturated aldehydes in one-pot, providing a broad range of secondary amines bearing a sp^3 C–Si bond *beta* to the nitrogen atom. The present catalysis is convenient and selective even in gram-scale synthesis. The ^{1}H NMR study clearly suggests a sequential hydrosilylation cascade under kinetic differentiation, and that the N-substituent has an impact on the catalytic reactivity and selectivity. Asymmetric induction by a chiral feature present in the substrate enables to synthesize enantioriched β-silylated secondary amines in good yields.



Scheme 4. a) Gram-scale synthesis of β-silylated amines. b) Fleming-Tamao oxidation of the silylated product. c) Diastereoselective β-silylative reduction of α,β-unsaturated aldimines in one-pot.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: reductive amination • Lewis acidic borane • hydrosilylation • α,β-unsaturated compounds • selectivity

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[10] In most catalytic entries in Table 1, N-silyl-(3-phenylpropyl)aniline as an undesired product was observed in 10~20%.

[11] In an attempt to enable a *direct* silylative reductive amination, a reaction of cinnamyaldehyde, aniline (1 equiv), and $PhMe_2SiH$ (2 equiv) in the presence of catalytic $B(C_6F_5)_3$ (5 mol%) was performed at 100 °C for 15 h in toluene, disclosing that neither enimine/enamine intermediates nor the β-silylated product **1** were formed.

[12] The above two reactions in Scheme 2 generated the undesired exhaustive reduction products in approximately 10% yields.

[13] The catalytic amount of an adduct of $B(C_6F_5)_3$ with N-phenyleneimine was observed by ^1H NMR during the catalytic turnovers, see: a) J. M. Blackwell, E. R. Sonmor, T. Scoccitti, W. E. Piers, *Org. Lett.* **2000**, *2*, 3921; b) J. M. Blackwell, W. E. Piers, M. Parvez, R. McDonald, *Organometallics* **2002**, *21*, 1400.

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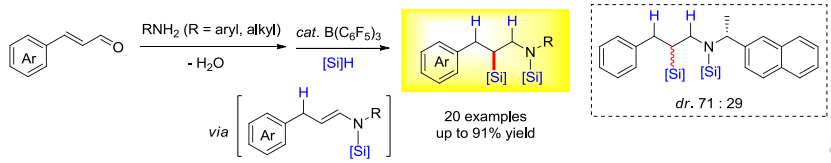

Silylative reductive amination of α,β-unsaturated aldehydes has been first realized under the borane catalysis, providing a wide range of combinatorial structures of secondary amines bearing a sp^3 C–Si bond *beta* to the nitrogen atom in high yields. Monitoring of the reaction progress revealed that the *N*-substituent of an amine unit has a significant impact on both reaction rate and regioselectivity.

Eunae Kim, Sehoon Park, Sukbok Chang**

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Title
Silylative Reductive Amination of α,β-Unsaturated Aldehydes: A Convenient Synthetic Route to β-Silylated Secondary Amines